REMARKS

Status of the Application

Claims 23, 27-30, 34-38, 44 and 45 were pending in the application at the time the Office Action was mailed. Claims 34-38 and 45 were withdrawn. Claims 23, 27-30 and 44 were rejected. No claims were allowed. Claims 23, 27-30, 34-38, 44 and 45 have been canceled. Claims 46-52 have been added. Therefore, claims 46-52 are presently before the Examiner for consideration. A Request for Continued Examination (RCE), a Request for a Retroactive Extension of Time, and the requisite fees are filed herewith.

The amendments made herein are made solely for responding to this Office Action and are not to be construed as acquiescing to the Examiner's position nor surrender of any subject matter. Applicants reserve the right to pursue the amended or canceled subject matter in one or more divisional or continuation applications. No new matter has been added by virtue of these amendments and entry is respectfully requested.

Claim Rejections under 35 U.S.C. § 102

Claims 23 and 27 were rejected under 35 U.S.C. 102(b) as being anticipated by Schlingensiepen et al. (EP 1,133,988, "Schlingensiepen V"). Claims 23 and 27 have been canceled herein solely to expedite prosecution, and new claims 46-52 have been added. Applicants submit that new claims 46-52 are novel over Schlingensiepen V, as this reference fails to disclose all claim limitations. The subject matter of new claims 46-52 is a combination of a TGF-beta2 oligonucleotide (e.g., an oligonucleotide of the sequence SEQ ID NO: 35) and specific types of cancer and the treatment of metastases, not primary tumors. Schlingensiepen V do not teach that SEQ ID NO: 35 (corresponding to SEQ ID NO: 5 in Schlingensiepen V) is effective in treating tumors. Schlingensiepen V discloses numerous oligonucleotides directed to different targets, and these oligonucleotides are used in the treatment of tumors, immune disorders, or improving organ or cell transplantation or cell expansion. Schlingensiepen V do not at all teach that SEQ ID NO: 35 is effective in treating tumors, and in particular, does not provide any hint that this sequence is effective in treating metastasis.

Applicants wish to emphasize that the claims are directed to inhibiting the formation of metastases in contrast to treating a primary tumor. As it is well known by a person skilled in the

art, medicaments that are effective in treating primary tumors are not necessarily effective in treating metastases. In addition, in the new claims, the type of cancer has been specified as colon carcinoma, colorectal carcinoma, pancreas carcinoma, prostate cancer or melanoma. Schlingensiepen V do not specify the tumor being treatable by SEQ ID NO: 35. It is known by a person skilled in the art that one compound is rarely effective in the treatment of any type of tumor. The same is relevant for the effect on metastases. Even if it is known that a compound is effective in inhibiting one type of metastases, it rarely or never is effective in any other type of metastasis. MIA for example inhibits the formation of metastases in melanoma treatment, but is not effective in inhibiting formation of metastases based on other primary tumors. Schlingensiepen V is completely silent on the effect of SEQ ID NO: 35 on the formation of metastases in the treatment of colon carcinoma, colorectal carcinoma, pancreas carcinoma, prostate cancer or melanoma.

Thus, Schlingensiepen V neither anticipate the subject matter of the new claims nor render them obvious, and therefore, the subject matter of the new claims is novel and inventive in view of Schlingensiepen V.

Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103

Claims 23, 27-30 and 44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Schlingensiepen et al. (WO 99/63975, "Schlingensiepen VI"). According to the Office Action:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the oligonucleotides shown in figure 1 of Schlingensiepen et al. to treat cancer, including colorectal carcinoma, pancreatic carcinoma and prostatic carcinoma. Several of the claimed sequences (particularly SEQ 10 NOs: 28, 29, 34, 35, 40 and 42) are found in this figure. One would have reason to use these sequences and would expect success in doing so because Schlingensiepen et al. teach that these sequences are suitable for use as medicaments and specifically contemplate their use in treating the types of cancers claimed (see claims 1, 3, 5, 12 and 13). While Schlingensiepen et al. do not explicitly teach that performing this method will provide the outcome of inhibiting formation of metastases, because Schlingensiepen et al. teach a method sharing the identical step of the claimed method that uses the same

sequences, performing this method is considered in the absence of factual evidence to the contrary to provide the claimed outcome.

Claims 23, 27-30, 34-38, 44 and 45 have been canceled solely to expedite proseuction. New claim 46 recites "[a] method for inhibiting the formation of metastases in treatment of colon carcinoma, colorectal carcinoma, pancreas carcinoma, prostate cancer or melanoma in a subject comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, and 48 to a subject, wherein said at least one oligonucleotide inhibits the formation of metastases in said subject." New claim 51 recites "A method of cancer treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, and 48 to a subject, wherein said at least one TGF-beta2 antisense oligonucleotide inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of prostate cancer, colon cancer, pancreatic cancer, melanoma and colorectal carcinoma." New claim 52 recites "[a] method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, and 48 to a subject, wherein said cancer is selected from the group consisting of prostate cancer, colon cancer, pancreatic cancer, melanoma and colorectal carcinoma." Applicants assert that new claims 46-52 are unobvious over Schlingensiepen VI. Not only does Schlingensiepen VI fail to teach or explicitly or implicitly suggest all claim limitations, Schlingensiepen VI fails to explicitly or implicitly suggest modifying its teachings to arrive at Applicants' invention.

First, Schlingensiepen VI do not teach that SEQ ID NO: 35 (corresponding to SEQ ID NO: 14 in Schlingensiepen VI) is effective in treating tumors. Schlingensiepen VI discloses numerous oligonucleotides directed to different targets, and these oligonucleotides are used in the treatment of tumors, inflammatory diseases or infectious diseases. It is shown that these oligonucleotides are able to stimulate the cytotoxic activity of lymphocytes towards tumor cells of cultured tumor cell lines. Although the oligonucleotides may be useful for the treatment of actual tumors, Schlingensiepen VI do not at all teach that SEQ ID NO: 35 is effective in treating

tumors, and does in particular not provide any hint that this sequence is effective in treating metastasis.

Second, new claims 46-52 are directed to inhibiting the formation of metastases in contrast to treating a primary tumor. As it is well known by a person skilled in the art, medicaments being effective in treating primary tumors are not necessarily effective in treating metastases. Schlingensiepen VI is completely silent on the effect of SEQ ID NO: 35 on the formation of metastases in the treatment of colon carcinoma, colorectal carcinoma, pancreas carcinoma, prostate cancer or melanoma. Therefore, the subject matter of the new set of claims is not obvious in view of Schlingensiepen VI.

Applicants assert that the methods of new claims 46-52 do not necessarily flow from the teachings of Schlingensiepen VI (or any of the previously cited prior art references), and that Schlingensiepen VI does not disclose performing the same steps using the same sequences resulting in the same therapeutic effect as recited in new claims 46-52. Applicants assert that the examiner has not provided sufficient rationale or evidence to show inherency and wish to again point to the following text copied directly from MPEP Section 2112:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).
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> Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but

> must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.
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> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients).

Applicants assert that the characteristic of metastases formation inhibition and treatment of colon carcinoma, colorectal carcinoma, pancreas carcinoma, prostate cancer or melanoma by the specific TGF-β2 antisense oligonucleotides currently claimed does not necessarily flow from the teachings of Schlingensiepen VI, and that new claims 46-52 are unobvious over Schlingensiepen VI.

In summary, Schlingensiepen VI does not disclose or even implicitly suggest the presently claimed *specific* selection of TGF-beta2 antisense oligonucleotides, which are able to inhibit the formation of metastasis and/or to treat metastasis. Applicants again assert that not all TGF-beta2 antisense oligonucleotides are able to inhibit the formation of metastasis, and that the presently claimed method of inhibiting the formation of metastases in the treatment of specific cancers in a subject involving the use of particular TGF-beta2 antisense oligonucleotides is not obvious in view of Schlingensiepen VI. New claims 46-52 are unobvious over Schlingensiepen VI, because not only does Schlingensiepen VI fail to teach or explicitly or implicitly suggest all claim limitations, Schlingensiepen VI fails to explicitly or implicitly suggest modifying its teachings to arrive at Applicants' invention.

Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

An RCE and the fee for a Three-Month Extension of Time are filed herewith. A credit card payment is made herewith for the required fees. However, the Commissioner for Patents and Trademarks is hereby authorized to charge any underpayment of fees or credit any overpayment of fees to Deposit Account No. 14-1437.

Respectfully submitted,

/Amy Dobbelaere/

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